Journal of Cardiology Cases 14 (2016) 69–70

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Editorial

Cryptogenic stroke prevention through venous thromboembolism prevention: Potential and truth in the advent of non-vitamin K antagonist oral anticoagulants

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disorder worldwide, having an estimated annual incidence of 0.1% and affecting 2–5% of the world's population during their lifetime. It has been previously reported that the incidence rate of DVT after orthopedic surgery is relatively lower among Japanese patients than among Caucasian patients [1]. However, until recently, there had been no systematic studies on the incidence rate of VTE, particularly in the Japanese population [2]. As VTE is drawing more attention, a systematic study on its treatment was published using data from the Japan VTE Treatment Registry (JAVA) in 2014 [3]. Although aggressive therapies were performed in the acute phase of PE, chronic anticoagulation therapy was not as strongly recommended as the European and US anticoagulation guidelines did.

PE treatment comprises anticoagulation, reperfusion, and inferior vena cava (IVC) filter placement. Reperfusion therapy includes systemic fibrinolysis, catheter-directed techniques, and the surgical removal of emboli. While remarkable progress has been made with interventional devices, anticoagulation therapy has also been developing since non-vitamin K antagonist oral anticoagulants (NOACs) were approved for VTE treatment. Phase III trials investigating the efficacy of NOACs such as apixaban, dabigatran, edoxaban, and rivaroxaban, for the treatment of VTE have been published [4–9]. In Japan, three NOACs, namely, edoxaban, rivaroxaban, and apixaban have been approved for VTE treatment to date. Clinical trials have proved that these NOACs are not inferior to conventional treatments, which include enoxaparin, unfractionated heparin, and warfarin. Enoxaparin is not widely used in Japan. Instead, fondaparinux, which is a synthetic pentasaccharide with anti-Xa activity, has been more commonly used in Japan. Clinical trial results suggested that NOACs were safer than warfarin with target prothrombin time-international normalization ratio (INR) 2–3 in terms of having lower incidence rates of major bleeding events, such as intracranial bleeding [10]. From the standpoint of long-term treatment planning, NOACs are expected to be a better choice than warfarin, when their price becomes more competitive with warfarin. This is because we can expect reliable efficacy and a reduced need for blood test monitoring [10]. Although there have been many studies on NOACs versus the aforementioned conventional therapies, the best NOAC for the treatment of PE and VTE has not been well studied.

In this report, Dr. Chitose described an interesting case, in which the use of rivaroxaban showed a better outcome as compared to edoxaban in an older female patient with DVT complicated by PE and an invaginated thrombus via a patent foramen ovale (PFO) [11]. Although this is a single case report, it provides some interesting points regarding patients with PE and PFO. How aggressive should we be in terms of performing invasive procedures such as catheter-directed thrombectomy or IVC filter placement? Should we administer systemic fibrinolysis therapy? How and which medications should we use for initial anticoagulation therapy and for maintaining the anticoagulation status? How should we treat patients with PFO to prevent stroke? Such questions must always be answered when caring for patients with PE and PFO.

The treatment for PE is time-sensitive. It is of the most importance to detect PE and keep hemodynamic stability with pressors and inotropes. At the same time, we need to evaluate the necessity of surgical or catheter-guided intervention such as thrombectomy and IVC filter placement. The initiation of anticoagulation is the most important step not only from the standpoint of acute treatment but also for chronic management. Intravenous administration of heparin followed by oral warfarin has been and still is the gold standard therapy for the treatment of PE. In the USA and European countries, subcutaneous enoxaparin injection is also a possible treatment choice. Although treatment with heparin and warfarin is well established and familiar to many clinicians, there are a few reasons for the possible superiority of NOACs. First, NOACs such as rivaroxaban have more stable pharmacokinetics profile than warfarin and pharmacodynamics. Second, some patients with the use of heparin, low-molecular weight heparin, or even fondaparinux are resistant to these drugs because their anticoagulant effects are mediated by antithrombin III. Moreover, these drugs have a potential to induce heparin-induced thrombocytopenia/thrombosis (HITT). HITT is a complicated and risky condition to induce clot formation even when platelet count is low. HITT might be recognized as the recurrence of PE. If the anticoagulant effect of NOACs appears immediately after their intake, they might provide us with solutions to the aforementioned problems that we have encountered in actual clinical settings.

The answer to the question "Which NOAC is the best for PE and VTE" remains uncertain. There have been no randomized controlled trials comparing the efficacy NOACs. This case report by Dr. Chitose suggests that rivaroxaban was superior to edoxaban, but this might simply have been due to the dosage difference as it was pointed out by the author. In Japan, the dosage of rivaroxaban approved for VTE treatment in the initial 3 weeks is twice as much

DOI of original article: http://dx.doi.org/10.1016/j.jccase.2016.03.020

http://dx.doi.org/10.1016/j.jccase.2016.06.009

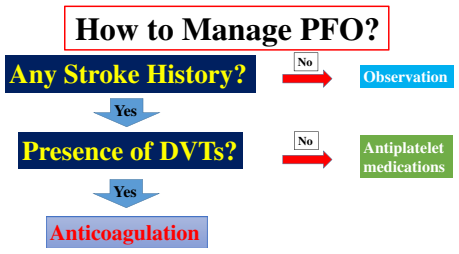

Fig. 1. The decision tree on management of a patent foramen ovale (PFO) patient based on presence of cryptogenic stroke or deep venous thromboembolism (DVT).

as that approved for stroke prevention for patients with atrial fibrillation. Contrarily, there is basically no dosage difference of edoxaban for these two clinical indications. It may be an interesting idea to switch from one NOAC to another if the first NOAC does not show any clinical efficacy. Although all NOACs approved for PE in Japan show anti-Xa inhibiting activities, subtle differences may exist among them that could affect their efficacies depending on the patient's biological condition. After the acute phase of PE, it is important to continue anticoagulation therapy for at least 3 months. Therefore, compliance and adherence are crucial to prevent recurrence of VTE just like stroke prevention for atrial fibrillation (AF) patients. It has been reported that actual adherence rates are much lower than those of clinical trials and that NOACs may still be beneficial in maintaining higher adherence rates compared with warfarin although the real world report did not support this idea in terms of stroke prevention for AF patients [12].

In this report, the patient's echocardiogram revealed an invaginated thrombus via PFO. Studies on PFO are gaining clinical interest because PFO is recognized as a possible cause of embolic stroke when its cause is undetermined. The foramen ovale does not close in approximately 25% of the general population although it usually does not cause any clinical problems [13]. If there is a paradoxical right to left shunt and a source of emboli, an embolic stroke, which is a cryptogenic stroke, could occur. DVT is often considered a risk factor for cryptogenic stroke. It has been reported that not only DVTs in the extremities but also DVTs in the pelvic veins can be a source of embolism [14]. Although PFO without any history of stroke is not an indication for anticoagulation, the latest guidelines from the American Heart Association and American Stroke Association recommend that anticoagulation should be initiated for patients with cryptogenic stroke and DVTs [15]. History of stroke and presence of DVTs are key points to the management of PFO patients (Fig. 1). According to the latest guidelines, aspirin is still the first-line treatment for cryptogenic stroke without DVTs; however, there are several ongoing clinical trials comparing the efficacy of NOACs with aspirin, such as NAVIGATE-ESUS and RE-SPECT ESUS trials (clinicaltrials.gov).

In conclusion, we expect NOACs to provide us with several options for treatment and they may improve the treatment effect, while heparin followed by warfarin is still the standard of care. We should carefully observe emerging differences in the efficacies of NOACs among various regions and countries [16]. Although published data from large trials should be appreciated, clinical physicians should appropriately apply these data according to each patient's profile.

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25 April 2016